Received: 11 September 2018 | Revised: 25 October 2018 | Accepted: 21 November 2018

DOI: 10.1002/hbm.24486

WILEY

RESEARCH ARTICLE

Distinct roles of brain activity and somatotopic representation in pathophysiology of focal dystonia

Kazumasa Uehara[1,2,3] | Shinichi Furuya[1,2,4] | Hidemi Numazawa[1] | Kahori Kita[1,2,5] | Takashi Sakamoto[6] | Takashi Hanakawa[1,2]

[1]Department of Advanced Neuroimaging, Integrative Brain Imaging Center (IBIC), National Center of Neurology and Psychiatry, Tokyo, Japan

[2]Musical Skill and Injury Center (MuSIC), Sophia University, Tokyo, Japan

[3]Research fellow of the Japan Society for the Promotion of Science, Tokyo, Japan

[4]Sony Computer Science Laboratories Inc. (Sony CSL), Tokyo, Japan

[5]Center for Frontier Medical Engineering, Chiba University, Chiba, Japan

[6]Department of Neurology, National Center of Neurology and Psychiatry, Tokyo, Japan

Correspondence
Takashi Hanakawa, MD, PhD, Department of Advanced Neuroimaging, Integrative Brain Imaging Center, National Center of Neurology and Psychiatry, 4-1-1, Ogawa-Higashi-Cho, Kodaira, Tokyo, 187-8551, Japan.
Email: hanakawa@ncnp.go.jp

Present address
Kazumasa Uehara, RIKEN CBS-TOYOTA Collaboration Center, RIKEN Center for Brain science, Saitama, Japan.

Funding information
JSPS KAKENHI, Grant/Award Number: 15H05357; National Center of Neurology and Psychiatry; AMED, KAKENHI, Grant/Award Numbers: 16H03306, 18H04960, 26120008; Japan Society for the Promotion of Science, Grant/Award Number: 26-119

Abstract

Two main neural mechanisms including loss of cortical inhibition and maladaptive plasticity have been thought to be involved in the pathophysiology of focal task-specific dystonia. Such loss of inhibition and maladaptive plasticity likely correspond to cortical overactivity and disorganized somatotopy, respectively. However, the most plausible mechanism of focal task-specific dystonia remains unclear. To address this question, we assessed brain activity and somatotopic representations of motor-related brain areas using functional MRI and behavioral measurement in healthy instrumentalists and patients with embouchure dystonia as an example of focal task-specific dystonia. Dystonic symptoms were measured as variability of fundamental frequency during long tone playing. We found no significant differences in brain activity between the embouchure dystonia and healthy wind instrumentalists in the motor-related areas. Assessment of somatotopy, however, revealed significant differences in the somatotopic representations of the mouth area for the right somatosensory cortex between the two groups. Multiple-regression analysis revealed brain activity in the primary motor and somatosensory cortices, cerebellum, and putamen was significantly associated with variability of fundamental frequency signals representing dystonic symptoms. Conversely, somatotopic representations in motor-related brain areas were not associated with variability of fundamental frequency signals in embouchure dystonia. The present findings suggest that abnormal motor-related network activity and aberrant somatotopy correlate with different aspects of mechanisms underlying focal task-specific dystonia.

KEYWORDS

brain activity, focal task-specific dystonia, functional magnetic resonance imaging, movement disorders, somatotopy

1 | INTRODUCTION

Focal task-specific dystonia (FTSD) is a movement disorder involving uncontrollable movement and abnormal posture in a part of the body, typically during over-practiced motor t asks (e.g., handwriting, instrument playing and sports) (Albanese et al., 2013; Furuya & Hanakawa, 2016; Hallett, 2011; Konczak & Abbruzzese, 2013). Several pathophysiological mechanisms have been proposed for FTSD: loss of cortical inhibition, maladaptive plasticity including disorganized somatotopy, and aberrant sensorimotor integration (Furuya & Hanakawa, 2016; Quartarone & Hallett, 2013; Rosenkranz et al., 2005; Stinear & Byblow, 2004a, 2004b). However, the most plausible mechanism remains unclear.

Previous studies suggest two distinct, yet not mutually exclusive, findings during motor tasks in FTSD. First, aberrant brain activity has been reported in motor-related networks including the cortical motor areas, basal ganglia and cerebellum (Furuya & Hanakawa, 2016; Hallett, 2011; Quartarone & Hallett, 2013). Several PET and functional MRI (fMRI) studies have reported overactivity in cortical and subcortical brain areas, while patients with FTSD perform dystonia-provoking tasks (Haslinger, Altenmüller, Castrop, Zimmer, & Dresel,

2010; Lerner et al., 2004; Preibisch, Berg, Hofmann, Solymosi, & Naumann, 2001; Zoons, Booij, Nederveen, Dijk, & Tijssen, 2011). Accordingly, transcranial magnetic stimulation (TMS) studies in FTSD reported excessive excitability (Stinear and Byblow, 2004a, 2004b; Beck et al., 2008), aberrantly reduced intracortical inhibition and elevated intracortical facilitation in the primary motor cortex (M1) (Furuya, Uehara, Sakamoto, & Hanakawa, 2018; Ridding, Sheean, Rothwell, Inzelberg, & Kujirai, 1995; Stinear & Byblow, 2004c). Such cortical overactivity supports the loss of inhibition theory. However, other studies have indicated reduced brain activity during motor performance in FTSD (Haslinger et al., 2005; Islam et al., 2009; Oga et al., 2002). Thus, although aberrant brain activity may be related to the pathophysiological mechanisms of FTSD, controversy remains.

Disorganization somatotopic representations of brain areas in FTSD is another expected finding in which the somatotopic organization of a dystonic body part may abnormally expand or overlap that of other body parts. Disorganized somatotopy is consistent with the characteristic symptom of "overflow" in FTSD (Albanese et al., 2013) and is supported by a primate model of focal dystonia (Byl, Merzenich, & Jenkins, 1996). Neuroimaging and neurophysiology studies have reported that patients with FTSD exhibit disorganized somatotopic representations of the affected body part within somatosensory areas (Hirata, Schulz, Altenmüller, Elbert, & Pantev, 2004; Mantel et al., 2016; Meunier et al., 2001; Weise et al., 2012) and also M1(Schabrun, Stinear, Byblow, & Ridding, 2009). However, most previous studies tested somatotopy using peripheral electrical stimulation without any motor task. Therefore, these findings may not reflect somatotopic representations associated with voluntary movement, which typically precedes overture of dystonic symptoms. Thus, it remains unclear whether aberrant somatotopy is associated with dystonic symptoms.

Importantly, it is unclear whether aberrant brain activity, disorganized body representation, or both, represent the primary pathophysiology of FTSD, for several reasons. First, few previous studies directly tested both brain activity and somatotopy using the same datasets during motor tasks. Second, imaging or physiology biomarkers for brain activity and somatotopical disorganization have not been connected with objective measures representing the severity of dystonic symptoms. To elucidate these issues, we examined patients with embouchure dystonia (ED) as an example of FTSD, using fMRI during both embouchure and somatotopy tasks. ED is a type of FTSD affecting the lip, jaw, tongue, facial, laryngeal, or masticatory muscles, such as involuntary tremor or lip-pulling while controlling air flow into the mouthpiece of a wind instrument such as trombone, trumpet, or horn (Frucht, 2009, 2016; Iltis et al., 2015; Termsarasab & Frucht, 2016). Previous imaging studies reported aberrant brain activity in sensorimotor areas while patients with ED blew into an MRI-compatible mouthpiece (Haslinger et al., 2010). Moreover, a tactile stimulation paradigm revealed abnormal somatotopic representations of the somatosensory cortex (S1) and cerebellum in patients with ED (Hirata et al., 2004; Mantel et al., 2016). Thus, the development of ED may disrupt both brain activity and somatotopic representations. However, it remains unclear which mechanism is most strongly correlated with the symptoms of ED.

Here, we investigated brain activity during an embouchure task and somatotopic representations during motor localizer tasks, and tested which better explained a behavioral marker representing dystonic symptoms in ED. For a reliable behavioral biomarker reflecting the severity of ED, we utilized a previous finding that patients with ED have greater fundamental frequency (F0) variability than healthy players (Lee, Furuya, Morise, Iltis, & Altenmüller, 2014; Morris, Norris, Perlmutter, & Mink, 2018). We used variability of F0 signals as an objective and quantitative marker representing symptoms in ED. We hypothesized that (1) brain activity and somatotopic representations in the sensorimotor areas would differ between ED and healthy wind instrumentalists, and (2) either brain activity or somatotopic representations, or both, would predict the loss of fine motor control representing variability of F0 signals.

2 | MATERIALS AND METHODS

2.1 | Participants

Fourteen patients with ED (mean age 43.1 ± 11.7 years, two females, one left-handed) and 14 age and gender-matched healthy wind instrumentalists as healthy controls (HCs; mean age 37.8 ± 10.8 years, two females) participated in this study. Participants' demographic characteristics are summarized in Table 1. Patients with ED were recruited at the National Center of Neurology and Psychiatry (NCNP) Hospital. Diagnosis of ED was made by experienced neurologists (T.S. and T.H.). All patients exhibited typical ED (tremor, crumpling, and pulling) in the lip, perioral, and/or jaw muscles while playing an instrument. Some patients had additional involvement of the tongue. Participants in both groups were wind instrumentalists who belonged to professional or amateur orchestras, music colleges, or freelance professional musicians. Exclusion criteria included a history of any neurological and neuropsychiatric disorders other than ED and any pharmacological intervention (e.g., neuroleptic drugs and botulinum toxin injection) within the past 3 months. Participants gave written informed consent prior to participation. The experimental protocol was approved by the ethics committee of NCNP.

2.2 | Experimental design

An fMRI experiment consisted of embouchure and control (straw) task fMRI and localizer task fMRI, based on blood oxygenation level-dependent (BOLD) signals. Behavioral measurement was performed outside the scanner room after MRI measurement on the same day.

2.3 | Behavioral experiment for quantification of acoustic signals

Methods for behavioral measurement (F0 variability) followed previously reported protocols (Lee et al., 2014). Participants played a long tone for approximately 8 s without vibrato at three pitches (low, middle and high pitch registers) using their own instruments. They were asked to maintain loudness and pitch as precisely as possible. Acoustic signals were recorded with a microphone in a silent room and sampled at 16-bit and 48.1-kHz for off-line analysis. Each participant performed 10 trials of each register (total 30 trials).

TABLE 1 Participants' demographic information and clinical characteristics of patients with ED and HC

	ID	Age range (yrs)	Gender	Instrument	Age when starting the instrument (yrs)	Duration of playing the instrument (yrs)	Daily practice in hours	Age at dystonia onset (yrs)	Duration of dystonia (yrs)	Affected register based on subjective feeling	Worst register based on F0 signals	Affected area
	ED1	60–70	M	Trombone	13	50	5	55	8	Low	Low	P,T,L
	ED2	40–50	M	Trombone	14	34	2	40	8	Low	Low	P
	ED3	20–30	M	Trumpet	12	13	3	13	12	Low	High	P
	ED4	40–50	M	Trombone	13	32	2	42	3	All	Low	P,T
	ED5	50–60	M	Trumpet	10	48	0.5	38	20	Low	High	P,T
	ED6	50–60	M	Saxophone	18	39	1	30	27	High	Low	P,J
	ED7	30–40	F	Flute	11	21	0	30	2	All	High	P,T,J
	ED8	40–50	M	Trombone	12	34	5	39	9	Low	Low	P,T
	ED9	40–50	M	Trumpet	10	36	1.5	39	7	Middle	High	P,J
	ED10	40–50	M	Trumpet	13	32	1.5	43	2	High	High	P,T
	ED11	30–40	M	Trombone	13	25	3	33	5	Low	Low	P
	ED12	20–30	F	Saxophone	11	12	1	18	5	All	Low	P,J
	ED13	30–40	M	Horn	9	18	0.5	25	6	All	Low	P,J,T,L
	ED14	40–50	M	Tuba	12	32	4	38	6	Low and middle	Low	P
Mean		43.1	12 M:2F		12.2	30.4	2.1	34.5	8.6			
SD		11.7			2.3	11.6	1.6	10.8	7.0			
	HC1	40–50	M	Trombone	13	36	3	–	–	–	Low	–
	HC2	40–50	M	Trumpet	11	34	2	–	–	–	High	–
	HC3	40–50	M	Trombone	13	36	3	–	–	–	Low	–
	HC4	40–50	M	Trombone	15	33	1	–	–	–	Low	–
	HC5	50–60	F	Flute	14	45	2	–	–	–	Middle	–
	HC6	20–30	F	Trumpet	14	10	2	–	–	–	High	–
	HC7	20–30	M	Trumpet	16	7	2	–	–	–	High	–
	HC8	30–40	M	Trombone	19	12	3	–	–	–	Low	–
	HC9	20–30	M	Horn	11	16	0.5	–	–	–	Low	–
	HC10	30–40	M	Trumpet	10	28	3	–	–	–	Low	–
	HC11	30–40	M	Saxophone	12	22	1.5	–	–	–	High	–
	HC12	30–40	M	Saxophone	13	25	1.5	–	–	–	High	–
	HC13	30–40	M	Trumpet	9	22	0.5	–	–	–	High	–
	HC14	40–50	M	Trombone	13	28	0.5	–	–	–	High	–
Mean		37.8	12 M:2F		13.1	25.3	1.8					
SD		10.8			2.7	11.2	1.0					

ED = Embouchure dystonia; HC = Healthy control players; M = male; F = female; P = Perioral muscle; T = Tongue; J = Jaw; L = Laryngeal.

2.4 | Embouchure and control task fMRI

The participants lay supine on a scanner bed, wearing an MRI-compatible head-set. Participants viewed visual stimuli projected onto a screen, through a mirror attached to the head coil. Stimulus presentation, including visual and auditory cues, was controlled on a personal computer and synchronized with fMRI scanning using Presentation software (Neurobehavioral Systems, California). During the embouchure-task fMRI, each participant performed a dystonia-provoking embouchure task in accord with a previously reported method (Haslinger et al., 2010). The task required participants to buzz a plastic mouthpiece at a pace of 1-Hz, synchronized with auditory cues. In the control motor task, participants blew through a plastic straw at the same pace as in the embouchure task. The participants underwent three fMRI runs, each lasting approximately 8 min; each run consisted of six blocks (20 s) of the same task (mouthpiece or straw), alternating with rest blocks (20 s) accompanied with visual fixation and 1-Hz auditory cues. Visual cues were used to prompt participants to buzz the mouthpiece, blow the straw, or remain at rest.

The plastic mouthpiece and straw (9 mm in internal diameter) were mounted on cardboard (Haslinger et al., 2010). The mouthpiece was chosen according to each participant's primary wind instrument. The internal diameter was 25, 15, 17, 17, and 31 mm for the trombone, trumpet, horn, flute, and tuba mouthpieces, respectively. The saxophone mouthpiece had 2–3 mm tip opening. Participants were instructed to hold the board using both hands with minimum effort, to support their upper limbs with the thorax and flex their elbow throughout the embouchure task fMRI. Participants were instructed to use minimal wrist movement to position the mouthpiece or the straw in front of their lip, in accord with a preparatory visual cue at the beginning of each block. Preparatory cues were displayed 2.5-s before the visual "Go" cue. A visual analog scale (VAS) ranging from 0 (no symptom) to 10 (worst symptom) was obtained after each fMRI run to check ED symptoms during the embouchure and control tasks.

2.5 | Functional localizer fMRI

All participants underwent functional localizer fMRI to assess somatotopic representations of the mouth and other body parts and to define volumes of interest (VOI) for assessing brain activity. Participants performed three voluntary motor tasks: (1) contraction of bilateral perioral muscles, (2) contraction of bilateral frontalis muscle, and (3) finger-thumb opposition movements with both hands. The localizer tasks were paced with auditory cues at 1 Hz, and visual cues prompted participants to move the instructed body part, or rest. Participants performed three fMRI runs, each lasting approximately 6 min; each run consisted of three 20-s blocks of the same task (mouth, forehead, or hand) alternating with 20-s rest blocks during which the visual fixation and 1 Hz auditory cues were presented.

The motivation for assessing the hand motor representation with the localizer fMRI was to define a reference location for Euclidean distances between the mouth and hand representations (Hirata et al., 2004; Morris et al., 2018) (see Section 2.8 for details).

2.6 | MRI data acquisition

For image acquisition, we used a 3-T MRI scanner (Magnetom Verio, Siemens, Erlangen, Germany) with a 32-channel phased array head coil. For both the embouchure/straw fMRI and localizer fMRI, functional imaging data were acquired using an echo planar imaging (EPI) sequence with the following parameters: repetition time (TR) = 2,500 ms; echo time (TE) = 30 ms; flip angle = 80°, field of view = 212 × 212 mm^2; with 40 axial slices; slice thickness = 3.2 mm with a 0.8 mm-gap; 3.3 × 3.3 × 4.0 mm voxel size, covering the whole brain. For anatomical registration, T1-weighted three-dimensional structural images were acquired using the magnetization prepared rapid gradient echo sequence with the following parameters: TR = 1,900 ms, TE = 2.52 ms, inversion time (TI) = 900 ms, flip angle = 9°, field of view = 250 × 250 mm^2, acquisition matrix = 256 × 256, slice thickness = 1 mm without gap, axial slice number = 192, and voxel size = 0.97 × 0.97 × 1.0 mm^3.

2.7 | Data analysis

2.7.1 | Behavioral measurement

To analyze F0 variability, we discarded the first 1 s of each recording according to a previously reported method (Lee et al., 2014). We extracted time-series of F0 signals from each recorded acoustic sound using a Tandem-Straight package (Kawahara & Morise, 2011; Kawahara, Takahashi, Morise, & Banno, 2009) with fast Fourier transform (FFT)-based convolution and custom-written code implemented in MATLAB R2015b (Mathworks, Inc., The United States). We computed mean and standard deviation (SD) of F0 with a moving time-window of 100 ms over the 3 s within a trial (i.e., from 1 to 4 s), then quantified the instability of F0 with coefficient of variation (CV; SD/mean × 100) across all windows.

2.7.2 | Preprocessing and statistical analysis for task-fMRI and functional localizer fMRI scan

Image preprocessing and statistical analyses were carried out using SPM 12 (http://www.fil.ion.ucl.ac.uk/spm/) implemented in MATLAB. The first four volumes from each run were discarded to ensure stable magnetization. Imaging data were spatially realigned to the first volume in the remaining time series. ArtRepair toolbox (http://cibsr.stanford.edu/tools/human-brain-project/artrepair-software.html) was used to correct for motion-related artifacts and noise spikes due to excessive head movement. Subsequently, slice timing correction, coregistration with structural images, normalization to the Montreal Neurological Institute (MNI) template and smoothing using isotropic Gaussian Kernel of 8 mm full-width at half-maximum (FWHM) were performed according to standard procedures.

We then computed a single-subject fixed-effects model using a general linear model (GLM). In the GLM analysis of embouchure-task fMRI, we used a boxcar function convolved with a canonical hemodynamic response function (HRF) for the following three conditions; Embouchure, Straw (control), and Rest. Global signal normalization was performed only between runs. Low frequency noise was removed using a high-pass filter with a cut-off of 128 s and serial correlations were adjusted using an auto-regression model. For each participant,

the following contrasts were created to produce contrast-weighted parameter estimate ($c * \beta$) maps: Embouchure versus Rest, and Embouchure versus Straw. In the GLM analysis of localizer fMRI, four conditions were modeled: Rest, Mouth, Forehead, and Hands. For each participant, contrasts of Mouth versus Rest, Forehead versus Rest, and Hands versus Rest were created.

Based on the previous studies, we had a clear hypothesis about brain regions associated with dystonia symptoms (Delmaire et al., 2005; Furuya et al., 2018; Granert, Peller, Jabusch, Altenmuller, & Siebner, 2011; Haslinger et al., 2010; Konczak & Abbruzzese, 2013; Kita, Rokicki, Furuya, Sakamoto, & Hanakawa, 2018; Løkkegaard et al., 2016; Moore, Gallea, Horovitz, & Hallett, 2012; Neychev, Gross, Lehericy, Hess, & Jinnah, 2011). We therefor ran the localizer fMRI to define VOIs. By capitalizing on the localizer fMRI, we used a functional VOI approach for the activity and somatotopy analyses because it has advantages over the voxel-wise group comparisons between the two groups, for which motor/somatosensory somatotopy may be differentially organized. Additionally, the VOI approach can adequately deal with the heavy multiple comparison problem (Mitsis, Iannetti, Smart, Tracey, & Wise, 2008; Poldrack, 2007). Using a VOI approach, we tested two hypotheses: (1) brain activity in sensorimotor-related areas would differ between ED patients and HCs and (2) somatotopic representations of the mouth area would be disorganized in ED patients. To assess somatotopy, we used a center of mass (CoM) analysis. Finally, we tested whether brain activity in the motor networks or disorganized somatotopy, or both, were associated with disrupted musical performance in ED, using F0 variability.

To define functional VOIs, we focused on bilateral M1, S1, cerebellum, and putamen (eight VOIs) because previous studies implicate these areas in the pathophysiology underlying FTSD (Delmaire et al., 2005; Haslinger et al., 2010; Neychev et al., 2011; Granert et al., 2011; Moore et al., 2012; Konczak & Abbruzzese, 2013; Løkkegaard et al., 2016; Furuya et al., 2018; Kita et al., 2018).

For functional VOIs, we first obtained activated clusters in each contrast of the localizer fMRI for each participant. To ensure that each activated cluster was restricted to each brain region of interest, we used the Human Motor Area Template (HMAT) (Mayka, Corcos, Leurgans, & Vaillancourt, 2006) for M1 and S1, AAL toolbox (Tzourio-Mazoyer et al., 2002) for the cerebellum, and the Basal Ganglia Human Area Template (BGHAT) (Prodoehl, Yu, Little, Abraham, & Vaillancourt, 2008) for the putamen. We built VOIs based on a one-sample *t*-test with a lenient threshold of $p < .05$ uncorrected for multiple comparisons for each participant, and the criterion of the activated clusters for the CoM analysis was set at more than four activated voxels within each brain region (Wu et al., 2005; Olman, Pickett, Schallmo, & Kimberley, 2012). In both ED and HC groups, we were unable to obtain voxels for the mouth representation of the putamen in three of 14 participants, even at the lenient statistical threshold. In these cases, functional VOIs were replaced with activations from each group-level result of other participants. Likewise, CoM for the putamen was also excluded from the final analysis because we could not identify activity clusters for the hand representation of the putamen from approximately half of the participants and the mouth representation of the putamen in three of 14 participants. In addition, CoMs of the forehead within each brain area were excluded from the final analysis because of high inter-individual variability. Therefore, we hereafter report the CoMs only for the mouth and hand within M1, S1, and cerebellum, all bilaterally. For confirmation, we ran a whole-brain analysis using a one-sample *t*-test at second-level random-effects analysis for both embouchure fMRI and localizer fMRI to identify brain activity cluster maps for each contrast across all participants. A whole-brain analysis with a two-way mixed design ANOVA was conducted to detect the main effects of "task" (two levels: Embouchure and Straw) and "group" (two levels: ED and HC) and their interaction. Both tests were thresholded at $p < .05$, family-wise error (FWE)-corrected for multiple comparisons. When necessary, we performed a small-volume correction (SVC) procedure utilizing the anatomically defined VOIs for M1, S1, cerebellum, and putamen, using the atlases described above.

2.8 | Statistics

The following statistical analyses were implemented using R environment (R 3.4.1, www.r-project.org/). Participants' demographic information was compared using a two-sample t-tests. To analyze group differences in mean CV of the F0 signals for each register, natural logarithmic (log)-transformation was performed to meet the assumption of normal distribution. We then performed a two-way mixed design ANOVA with "group" (two levels: ED and HC) as the between-subject factor and "pitch" (three levels: low, middle, and high pitch) as the within-subject factor. Additionally, mean CV of the F0 signals for the worst pitch, which was treated as the dependent variable for a multiple regression analysis (see below), was compared between ED patients and HC using a two-sample *t*-test.

To assess group differences in mean brain activity (i.e., $c * \beta$ values) within each VOI across conditions and groups, we used a two-way mixed design ANOVA. "Group" (two levels: ED and HC) was treated as the between-subject factor. "Task" (two levels: Embouchure and Straw) was treated as the within-subject factor.

To assess group-wise differences of the mean CoMs in the mouth and hand representations in M1, S1, and the cerebellum, the stereotaxic coordinates of CoM (i.e., x-, y-, and z-spaces) were compared with a two-way mixed design ANOVA with "group" (two levels: ED and HC) as the between-subjects factor and "somatotopy" (two levels: mouth and hand) as the within-subject factor for each coordinate of CoM in each brain area. For the ANOVAs, post-hoc tests were performed using Benjamini–Hochberg multiple comparisons (Benjamini & Hochberg, 1995) whenever "within-subject factor" or an interaction between "between-subject factor" and "within-subject factor" was significant.

The primary goal of this study was to assess how brain activity induced by buzzing a plastic mouthpiece or the somatotopic representation of the mouth area could account for dystonia symptoms (i.e., fluctuation of F0 signals) in ED patients. We performed a stepwise multiple linear regression analysis with bi-directional elimination (i.e., forward and backward) from two perspectives: brain activity and somatotopic representation. In modeling with brain activity, the individual's $c * \beta$ values from eight VOIs (M1, S1, cerebellum, and putamen representations of the mouth area, all bilaterally) were the independent variables, while individual's log-transferred CV of F0

signals was the dependent variable. In modeling with somatotopic representations of the mouth area, we first calculated the Euclidean distance of CoMs in 3D space between the hand and mouth for each participant for each brain area, except for the bilateral putamen where CoM was not reliably computed. These Euclidean distance values were treated as the independent variables and individual's log-transferred CV of F0 signals was treated as the dependent variable. We chose the most unstable pitch (i.e., the pitch showing the highest CV) of the three pitches accompanied by dystonia symptoms in ED patients. The independent variables were tested for collinearity by confirming the variance inflation factor (VIF). An independent variable showing VIF > 5 indicated multicollinearity (O'Brien, 2007). We found that VIF values for the independent variables were less than 5, indicating no substantial multicollinearity. The goodness of the fitting model was expressed as R^2 and the significance of the modeling was assessed using an *F*-test. Moreover, using leave-one-out cross-validation (LOOCV), we validated the multiple regression models' ability to predict the variability of F0 signals to resolve over-fitting problems. Practically, one subject's data were used as test data, while the remaining subjects' data were used as training data for each validation fold. All statistical effects were tested at a significance level of $p < .05$.

3 | RESULTS

3.1 | Participants' demographic characteristics

A two-sample *t*-test did not identify between-group differences in age at enrollment ($t = 1.18$, $p = .24$), age at which participants began playing an instrument ($t = -0.95$, $p = .34$), duration of playing an instrument ($t = 1.19$, p = .24) or duration of daily practice in hours ($t = 0.6$, $p = .53$) (Table 1).

3.2 | F0 variability

A two-way ANOVA revealed significantly greater F0 variability in ED patients than in HCs ($F_{1,26} = 6.18$, $p = .01$) (Figure 1b). Moreover, a two-sample *t*-test revealed that F0 variability in the worst pitch within the three registers, which fed into the multiple regression analyses, was significantly greater in ED patients than in HCs ($t = 2.23$, $p = .03$) (Figure 1c). These results supported and replicated the instability of F0 signals in ED.

3.3 | Somatotopic representations assessed by the localizer task fMRI

Mean (*SD*) CoMs for the mouth and hand areas in M1, S1, and cerebellum are summarized in Figure 2 and Table 2. Two-way ANOVAs for CoM of the y and z-spaces revealed significant group-by-somatotopy interactions in the right S1 (y-space: $F_{1,26} = 6.23$, $p = .01$, z-space: $F_{1,26} = 5.18$, $p = .02$). Post hoc testing for CoM of y- and z-spaces revealed that CoM at the y-space in the mouth area of the right S1 significantly differed between ED patients and HCs ($p = .03$). Likewise, the CoM in the z-space showed a trend toward a difference between ED patients and HC ($p = .07$). Specifically, the mouth representation of right S1 in ED patients was located lateral and superior to that in HC. We found no significant differences in CoM between ED patients and HC, and no significant group-by-somatotopy interactions in other brain areas.

3.4 | Brain activity during embouchure and straw tasks

VAS was 3.9 ± 2.8 (mean $\pm$ *SD*) during the embouchure task fMRI and 0 ± 0 during the control (Straw) task. Specifically, 12 out of the 14 ED patients reported involuntary tremor and muscle contraction, lip-pulling or tongue stopping during the embouchure task fMRI, but not during the control task.

For VOI analysis of brain activity, a two-way mixed design ANOVA revealed a main effect of task ($F_{1,26} > 8.27$, $p < .01$ for all comparisons) in all VOIs, except for the right cerebellar VOI ($F_{1,26} = 0.07$, $p = .78$). However, the analysis revealed no main effect of group ($F_{1,26} < 2.06$, $p > .05$ for all comparisons) or any group-by-task interactions ($F_{1,26} < 2.00$, $p > .05$ for all comparisons) in each VOI (Figure 3). Consistently, a confirmatory whole-brain analysis revealed embouchure task-related brain activity (Haslinger et al., 2010), but failed to show group main effects or group-by-task interactions (Supporting Information Table S1).

3.5 | Multiple regression analysis

Multiple linear regression was performed in a stepwise manner for predicting the fluctuation of F0 signals, using either brain activity during the embouchure task or somatotopic representations (i.e., CoM) during the localizer task as explanatory variables. With Shapiro–Wilk tests, we found that raw F0 variability did not meet the normal distribution ($p < .05$). After log-transformation, we confirmed that log-transformed F0 variability followed normal distribution ($p > .05$). For the model using brain activity, the LOOCV confirmed that the regression model was able to predict the observed F0 variability with 73.4% accuracy. The brain activity model accounted for the F0 fluctuations in ED ($F_{4,9} = 6.22$, $p = .01$, $R^2 = 0.73$) using the right M1 ($\beta = 0.36$, $p = .004$) and left putamen ($\beta = 0.19$, $p = .03$), the right S1 ($\beta = -0.50$, $p = .003$) and left cerebellum ($\beta = -0.18$, $p = .009$). In contrast, the model using somatotopic representations failed to reliably predict the observed F0 variability (accuracy was 33.2%) in the LOOCV analysis.

4 | DISCUSSION

It is widely accepted that cortical and subcortical sensorimotor areas are involved in FTSD (Furuya & Hanakawa, 2016; Hallett, 2011; Quartarone & Hallett, 2013; Quartarone & Pisani, 2011). However, no previous studies provided direct evidence for an association between brain activity or somatotopic organization and a quantitative measure of dystonic symptoms using the same data set. To address this question, we designed the present study using task-fMRI and behavioral measurement in patients with ED. We assessed brain activity and somatotopy using fMRI data. Importantly, examining ED patients has

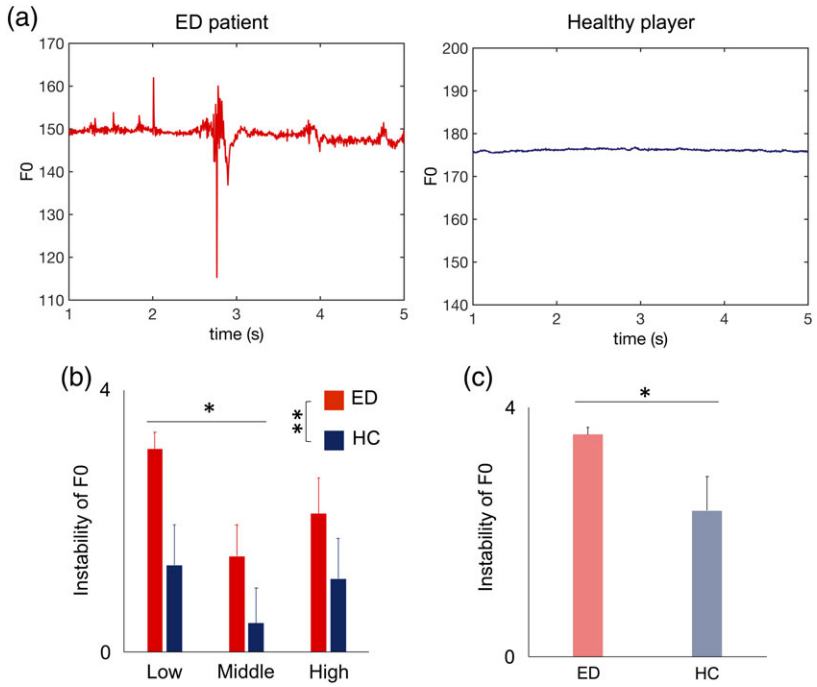

FIGURE 1 Fluctuation of F0 signals while playing a brass instrument. (a) Typical waveforms of F0 signals in time-series obtained from one representative embouchure dystonia patient (red) and a healthy control player (blue). The F0 time-series in an ED patient was more unstable than that of an HC participant. (b) The group mean CV values of F0 signals at low, middle and high pitch registers. (c) The group mean CV values of F0 signals obtained from the worst pitch register. High numbers indicate more fluctuation of F0. ED and HC indicate embouchure dystonia and healthy players, respectively. Error bars reflect standard errors (SE). Asterisks denote significant comparisons: * $p < .05$, ** $p < .001$ [Color figure can be viewed at wileyonlinelibrary.com]

an advantage over examining focal *hand* dystonia patients for somatotopy analysis; it would be difficult to measure somatotopic representations of the affected fingers, which often differ across patients, in focal *hand* dystonia, because the representations of each finger are topographically close or overlapping (Ejaz, Hamada, & Diedrichsen, 2015). This would be particularly problematic in *hand* dystonia affecting neighboring fingers since one previous study showed that hand motor somatotopy could not be differentiated between writer's cramp patients and HCs (Weise et al., 2012). Such methodological difficulties in assessing finger somatotopy may explain why previous somatotopy studies of hand dystonia used sensory stimulation. In contrast to focal *hand* dystonia, examining patients with ED allowed us to assess gross somatotopic representations between the mouth and hand areas because the distance between the representations of the mouth and hand is relatively large, even with the current spatial resolution. Hence, we believe that the present study provided relatively precise data regarding altered somatotopic representations in ED.

Our results revealed several novel findings. First, although brain activity in the sensorimotor areas did not differ between ED and HC, brain activity in M1, S1, putamen, and cerebellum was associated with a measure of dystonic symptoms representing disrupted musical performance (i.e., higher F0 variability) in ED. Second, the somatotopic representation of S1 significantly differed between ED and HC, but somatotopic representations in sensorimotor brain areas were not obviously associated with disrupted musical performance in ED. Taken together, abnormal motor-related network activity and aberrant somatotopy appear to contribute to different aspects of the mechanisms underlying ED.

We replicated the previous finding that patients with ED exhibited greater variability of F0 signals than HCs during tone production (Lee et al., 2014; Morris et al., 2018). Those pioneering studies demonstrated that variability of F0 signals during tone production serves as a hallmark of ED (Lee et al., 2014; Morris et al., 2018), supporting the notion that quantification of F0 variability reflects dystonic symptoms of ED. Although the neural correlates of this symptom had not previously been identified, we found a correlation between F0 variability and brain activity, lending further support to the notion that F0 variability is a reliable behavioral measure for assessing individual differences in ED severity.

4.1 | Brain activity is involved in dystonic motor symptoms

Multiple regression analyses revealed that activity in the left putamen contributed to the prediction of F0 variability in ED patients. Accumulating evidence suggests that dystonia can arise from functional or anatomical changes in the basal ganglia (including the putamen) in both humans and experimental animals (Black, Ongür, & Perlmutter, 1998; Delmaire et al., 2005; Bostan & Strick, 2010; Granert et al., 2011; Hallett, 2011; LeDoux, 2011; Neychev et al., 2011; Bostan, Dum, & Strick, 2013; Simonyan, Cho, Hamzehei Sichani, Rubien-Thomas, & Hallett, 2017; Kita et al., 2018). For example, patients with musician's dystonia involving the hands exhibit abnormally increased resting state network connectivity in the putamen compared with healthy musicians (Kita et al., 2018). Overall, these findings provide

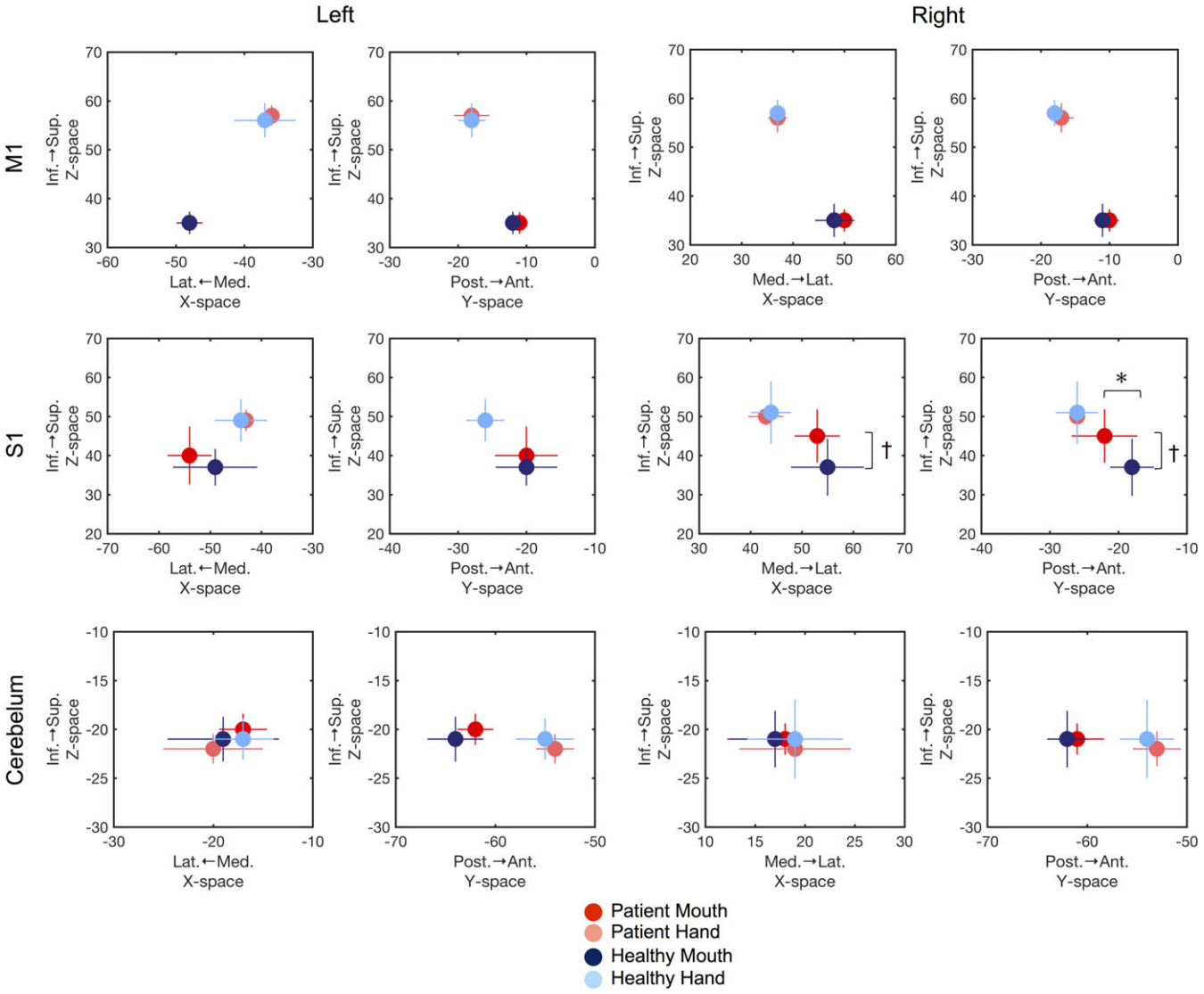

FIGURE 2 Somatotopic representations of mouth and hand within M1, S1, and cerebellum in the ED and HC groups. Inferior–superior (z-space) plotted against medial-lateral (x-space) and anterior–posterior (y-space) for the group mean coordinates. The coordinates (x, y, z) conform to MNI coordinates. The CoM of the mouth area in the right S1 significantly differed between ED and HC. See Table 2 for detailed information. Error bars reflect standard deviation (*SD*). Asterisks denote significant comparisons: * $p < .05$. The dagger indicates a difference trend between the groups ($p = .07$). Note that the CoMs of the forehead within the all brain regions and those within the putamen were excluded from this figure due to extensively high inter-individual variability of the CoMs, and due to participants exhibiting none of spatial characteristics of CoMs [Color figure can be viewed at wileyonlinelibrary.com]

converging evidence that putaminal dysfunction is associated with dystonic symptoms of FTSD.

Similarly, our regression model supported cerebellar involvement in disrupted motor performance in ED. Although the cerebellum is not traditionally considered to play a key role in FTSD, burgeoning evidence highlights cerebellar involvement in the pathophysiology of dystonia. "Tottering mice" studies have revealed that aberrant cerebellar activity drives dystonic movements (Chen et al., 2009; Pizoli, Jinnah, Billingsley, & Hess, 2002). Specifically, a genetically engineered rodent model of dystonia exhibits involuntary muscle activity as well as tremor, which become coherent with electrophysiological oscillations in the cerebellum (Chen et al., 2009). Extending our understanding of cerebellar involvement in FTSD requires consideration of the cerebellar functions in motor control. Intensive and repetitive training of a specific body part is typically necessary for sensorimotor skill learning. However, such training can cause maladaptive changes in the sensorimotor system, leading to FTSD (Byl et al., 1996; Furuya & Altenmüller, 2015; Furuya & Hanakawa, 2016; Quartarone & Hallett, 2013). The cerebellum plays an interactive role in motor learning and task-specific "internal models" (Hubsch et al., 2013; Imamizu & Kawato, 2012; Kawato, 1999). It is possible that maladaptive plastic changes in the cerebellum disrupt task-specific internal models involving an instrument play in FTSD.

In addition to the subcortical areas, M1 and S1 activity accounted for disrupted musical performance in ED in the regression model. There is a broad consensus that M1 and S1 play a key role in the pathophysiology of dystonia (Murase et al., 2000; Stinear & Byblow, 2004c; Tamura et al., 2009; Hallett, 2011; Quartarone & Hallett, 2013; Furuya, Nitsche, Paulus, & Altenmüller, 2014; Furuya et al., 2018; Furuya & Hanakawa, 2016). The most plausible

TABLE 2 Mean CoM for each body part within each brain area with *SD* in patients with ED and HC

	MNI coordinates		
Region	***x***	***y***	***z***
ED group			
Right M1			
Mouth	50 (2.0)	−10 (1.4)	35 (2.3)
Hand	37 (1.8)	−17 (1.8)	56 (3.0)
Left M1			
Mouth	−48 (1.9)	−11 (1.0)	35 (2.2)
Hand	−36 (1.2)	−18 (2.6)	57 (2.1)
Right S1			
Mouth	53 (4.4)	−22 (4.8) *	45 (6.8) †p = .07
Hand	43 (3.4)	−26 (1.1)	50 (2.3)
Left S1			
Mouth	−54 (4.3)	−20 (4.6)	40 (7.4)
Hand	−43 (1.9)	−26 (1.3)	49 (2.7)
Right cerebellum			
Mouth	18 (5.8)	−61 (2.7)	−21 (1.6)
Hand	19 (5.6)	−53 (2.4)	−22 (1.8)
Left cerebellum			
Mouth	−17 (2.4)	−62 (1.8)	−20 (1.6)
Hand	−20 (5.0)	−54 (1.9)	−22 (1.5)
HC group			
Right M1			
Mouth	48 (3.7)	−11 (1.2)	35 (3.4)
Hand	37 (1.5)	−18 (1.2)	57 (2.7)
Left M1			
Mouth	−48 (1.6)	−12 (0.5)	35 (2.3)
Hand	−37 (4.5)	−18 (2.0)	56 (3.5)
Right S1			
Mouth	55 (7.1)	−18 (3.2)	37 (7.3)
Hand	44 (3.9)	−26 (3.1)	51 (8.0)
Left S1			
Mouth	−49 (8.2)	−20 (4.5)	37 (4.7)
Hand	−44 (5.1)	−26 (2.8)	49 (5.4)
Right cerebellum			
Mouth	17 (5.1)	−62 (2.0)	−21 (2.9)
Hand	19 (4.8)	−54 (2.7)	−21 (4.0)
Left cerebellum			
Mouth	−19 (5.6)	−64 (2.8)	−21 (2.3)
Hand	−17 (3.1)	−55 (2.9)	−21 (2.1)

Note: Asterisk denotes significant group difference at $p < .05$.

candidate mechanism is the loss of inhibition at the level of M1 and S1. Our recent TMS study examined pianists with FTSD of the hand, revealing aberrantly reduced short-interval intracortical inhibition and elevated intracortical facilitation, associated with temporal imprecision and sluggish finger movement transition while playing the piano (Furuya et al., 2018). These discoveries suggest that overactivity in M1, corresponding to the loss of inhibition, may be related to the loss of dexterity in musician's dystonia. In the present study, although no significant group-wise differences existed in M1 activity, ED patients exhibited a trend toward overactivity in M1 during the embouchure task. Overactivity in M1, even at a sub-threshold level, may be associated with disrupted musical performance in ED. In contrast to M1, clear and feasible descriptions of the involvement of S1 dysfunction in dystonia are scarce (Konczak & Abbruzzese, 2013). However, the somatosensory cortex is likely to gate movement-related sensory inputs for filtering out redundant inputs reducing irrelevant information. This gating system plays an important role in organized movement (Lei & Perez, 2017; Macerollo, Brown, Kilner, & Chen, 2018; Seki & Fetz, 2012). Writer's cramp has been found to involve impaired sensory gating function at S1 during motor preparation (Murase et al., 2000). The association between S1 activity and musical performance in ED patients in the current study suggests that dysfunction of sensory gating may also exist in ED.

The present findings indicated that multiple sensorimotor-related areas including M1, S1, putamen, and cerebellum could be collectively responsible for FTSD. One interpretation for the neural mechanisms underlying FTSD is that dystonic symptoms may emerge as a manifestation of network disorders. Several MRI studies demonstrated that ED patients showed aberrant resting state networks (Haslinger et al., 2017) and laryngeal dystonia patients had greater sensorimotor, cerebellar and putaminal involvement in abnormal sensory discrimination (Termsarasab et al., 2016). Dysfunctional influence from M1 to the putamen, as well as to the cerebellum, was found during a finger tapping task in an effective connectivity study of writer's cramp using dynamic casual modeling of fMRI data (Rothkirch et al., 2018). This evidence suggests that interactions of multiple brain areas are likely to be related to the manifestation of dystonia.

4.2 | Aberrant somatotopy in embouchure dystonia

Previous imaging studies reported aberrant somatotopy in ED, demonstrating that the distance between the lip and hand in the somatosensory area in ED patients was significantly decreased (Hirata et al., 2004) or increased (Mantel et al., 2016) relative to HC. Consistent with these previous reports, we found that ED patients exhibited a shorter distance between the hand and mouth areas in the right S1 than that in HC. These findings suggest that the somatotopic representations in S1 are altered in ED, whereas M1 likely remains intact with regard to somatotopic organization. However, it is unclear why the present findings revealed changes in somatotopic representations only in S1 as a group-wise difference. We propose that repetitive sensory inputs and/or dedifferentiation of sensory feedback from the affected body part may induce malplasticity-based S1 remodeling. This assumption is supported by a previous study using an animal model of dystonia, in which rapid, repetitive and highly stereotyped movements applied in a learning context degraded the somatotopic representation, causing overlap and loss of differentiation in the hand skin representation in S1 (Byl et al., 1996).

In contrast to brain activity, we found no significant relationship between somatotopic representations and disrupted musical performance in ED. This finding raises the question of why we failed to observe the involvement of somatotopic representations, despite the existence of a group-wise difference, in dystonic motor symptoms. According to previous literature (Furuya & Hanakawa, 2016), reduction of surround inhibition and/or loss of inhibition may spread from

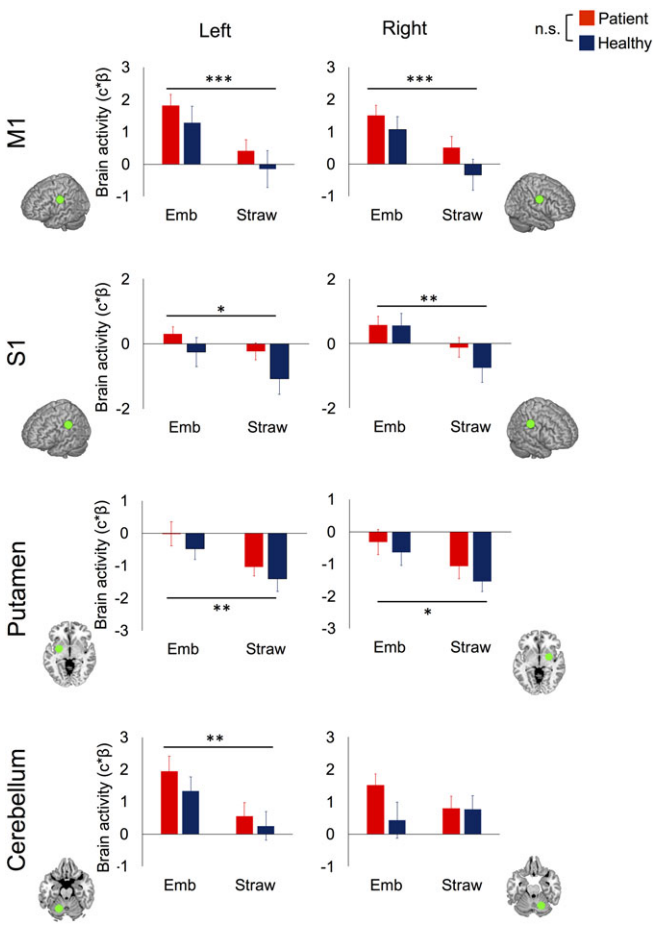

FIGURE 3 Brain activity during the dystonia-provoking task based on VOI analysis. The group mean $c * \beta$ values (i.e., brain activity) within each VOI during the dystonia-provoking task in the ED and HC groups. Emb indicates the embouchure task. Error bars reflect standard errors (*SE*). Asterisks denote significant comparisons: $*p < .05$, $**p < .01$, $***p < .001$ [Color figure can be viewed at wileyonlinelibrary.com]

the sensorimotor-related brain areas responsible for a specific body part to adjacent portions. Therefore, it is possible that the reduction of surrounding inhibition and/or loss of inhibition is a primary triggering factor for FTSD, whereas malplastic reorganization of somatotopy is a secondary change. This notion explains the present finding that malplastic reorganization of somatotopy was less likely to be involved in dystonic motor symptoms in FTSD.

4.3 | Study limitations

For the behavioral measure, the present study used F0 variability as an objective measure representing dystonic motor symptoms. However, dystonic motor symptoms are influenced by various factors such as severity, number of affected muscles, and playing strategy, including compensatory actions. Thus, inferences from the multiple-regression analyses are limited to the dystonic symptoms reflected by F0. Indeed, other behavior measurements are becoming available such as MRI scans capturing mouth and tongue movements (Iltis et al., 2016) and pressure on a mouthpiece while playing an instrument. Correlations between brain activity/somatotopy and these behavior measurements should be tested in future studies.

We used Euclidean distance to quantify the distance between the hand and mouth representations in M1 and S1. An alternative measure is geodesic distance, which is the shortest path along the surface connecting between two surface points, and is calculated using a cortical surface model (Margulies et al., 2016). Geodesic distance is suitable as a measure of the distance between two representations when they are separated by gyri and sulci. We used Euclidean distance because the cortical representations of the hand and mouth M1 are both located on the precentral gyrus. The hand and mouth S1 are located on the postcentral gyrus. Thus, the Euclidean distance should accurately quantify the distance between the mouth and hand representations of M1 and those of S1. Nonetheless, geodesic distance may be useful to probe a subtle difference in the somatotopic representations separated by gyri or sulci in future FTSD studies.

5 | CONCLUSIONS

Compared with healthy musicians, we found aberrant somatotopy, but not abnormal network activity, in musicians with ED. Counterintuitively, the results revealed that brain activity in multiple brain areas, including the right M1/S1, and the left putamen and cerebellum, but not altered somatotopic representations, were associated with symptoms of FTSD. It is likely that aberrant network activity and altered somatotopy are associated with different aspects of dystonic symptoms. The present findings revealed distinct roles of brain activity and somatotopy in the pathophysiology of FTSD. Thus, our results provide a missing link between previous neuroimaging findings and behavioral abnormality in FTSD. Likewise, the present study is clinically relevant, providing clues related not only to the diagnosis of FTSD but also to targets of noninvasive brain stimulation and neurofeedback, contributing to the development of new treatments.

ACKNOWLEDGMENTS

We thank all of the musicians who participated in this study and Benjamin Knight, MSc., from Edanz Group for editing a draft of this manuscript. This study was supported by a postdoctoral fellowship from the Japan Society for the Promotion of Science (JSPS) (26-119) to KU, a Brain Mapping by Integrated Neurotechnologies for Disease Studies (Brain/MINDS) grant from AMED, KAKENHI (26120008, 18H04960 and 16H03306) from MEXT, an Intramural Research Grant for Neurological and Psychiatric Disorders of National Center of Neurology and Psychiatry to TH and JSPS KAKENHI Grants-in-Aid for Young Scientists (A) (15H05357) to KK.

AUTHOR CONTRIBUTIONS

KU, SF, HN, KK, TS, and TH designed research and interpretation of data; KU, HN performed data collection; TH and TS performed clinical evaluation; KU and NH carried out data analyses; KU, TH wrote the manuscript; All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

ORCID

Kazumasa Uehara https://orcid.org/0000-0003-2350-8694

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How to cite this article: Uehara K, Furuya S, Numazawa H, Kita K, Sakamoto T, Hanakawa T. Distinct roles of brain activity and somatotopic representation in pathophysiology of focal dystonia. *Hum Brain Mapp*. 2019;40:1738–1749. https://doi.org/10.1002/hbm.24486